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Scutellaria barbata: A Review of Chemical Constituents, Pharmacological Activities and Clinical Application.

Scutellaria barbata: A Review of Chemical Constituents, Pharmacological Activities and Clinical Application

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Abstract:

Scutellaria barbata has a long history of medical use in Traditional Chinese Medicine for clearing away heat and toxic material, promoting blood circulation and removing blood stasis, and inducing diuresis to reduce edema. Recent pharmacology investigations have provided evidence for its anti-cancer, bacteriostasis, anti-virus, anti-inflammation, anti-oxidation and immunity enhancement properties. The efficacy of activating blood circulation and removing blood stasis has unique advantages in the treatment of cardiovascular and cerebrovascular diseases. A total of 84 compounds have been isolated from *S. barbata* and characterized mainly as flavonoids, diterpenoids, followed by polysaccharide, volatile oil and steroids. Peer-reviewed articles published over the last few years were gathered by consulting the databases PubMed, Elsevier, Springer and Chinese Herbal Classics. This review mainly focuses on the pharmacologically active constituents isolated from *S. barbata*， which have been subjected to *in vitro* and/or *in vivo* studies. Although the chemical components, pharmacological activities, toxicology, clinical applications and mechanisms of action of *S. barbata* have been investigated, many constituents remain unknown. Further investigations are required to investigate the medicinal properties of *S. barbata.*

Keywords: Traditional Chinese Medicine, *Scutellaria barbata*, pharmacology, toxicology, clinical application

1. Introduction

Scutellaria barbata is a perennial herb belonging to the family Lamiaceae, also known as Ban-zhi-lian (barbat sskullcap) in Traditional Chinese Medicine, and mainly grows throughout southern China and is a compoment of numerous medicinal formulas traditionally used in China and Kore[1]. *S. barbata* is used for the treatment of inflamed throad, severe pain, edema, jaundice, snake bite etc. Due to its ability in clearing away heat and toxic material, promoting blood circulation for removing blood stasis, and inducing diuresis to reduce edema[2]. Pharmacological studies have provided evidence for its anti-tumor, anti-oxidation, anti-bacterial, anti-inflammatory, anti-virus and immunonodulatory activities[3]. Clinically, the main indications of *S. barbata*is are for the treatment of sore throat, jaundice, hepatitis and adjuvant treatment of cancer[4]. At present, the research and application of the antitumor activity mainly focus on the crude extract or the parts extracted from *S. barbata*[5]. For example, the total flavonoids from *Scutellarin barbata* (TF-SB) can suppress the growth of various tumor cells via several specific signaling pathways[6]. *S. barbata* polysaccharide (SPS) inhibited the proliferation of lung adenocarcinoma cells by inhibiting the C-met pathway[7]. Scutellarein, a flavonoid monomer found in *S. barbata,* induced mitochondrial-mediated intrinsic apoptosis selectively in malignant cells[8]. Its function in activating blood circulation and removing blood stasis has important implications for the prevention and treatment of cardiovascular and cerebrovascular diseases[9]. Experiments have proved that activating blood circulation and removing blood stasis has certain effects on anti-thrombosis, improves the function of vascular endothelial cells, regulates blood lipids, displays anti-oxidation properties and eliminates free radicals[10].

Due to the versatile traditional medicinal uses of *S. barbata*, an increasing number of phytochemical studies have been conducted. *S. barbata* contains a large number of alkaloids, flavones, steroids and polysaccharides and other constituents[11]. In recent years, a large number of studies have been published on the active constituents of *S. barbata.* Four active components of total flavonoids of *S. barbata* were analyzed, including scutellarin, isoscutellarein-8-O-glucuronide, isoscutellerin and luteolin[12]. Some other compounds were also isolated and have been identified as, coumaric acid, cinnamic acid, protocatechuic acid, vanillic acid and scutellarin[13-16]. The contents of scutellarin and apigenin in *S. barbata* from 12 different habitats were in the range of

0.03% - 0.39% and 0.02% - 0.3%, respectively[17]. The present review is focused on ethnopharmacological uses, as well as the phytochemical, pharmacological, toxicological and clinical uses of *S. barbata*. The main chemical constituents and pharmacological activities of *S. barbata* were shown in Table 1 and Table 2, respectively.

2. Chemical Composition

2.1 Flavanoids

Flavonoids are one of the main physiological components *S. barbata*[18] and scutellarein, scutellarin, carthamidin and isocarthamidin have been identified [19]. The above ground part contains wogonin, naringenin, apigenin, hispidulin, eriodictyol, luteolin, 7-hydroxy-5, 8-dimethoxyflavone, 4'-hydroxywogonin, 5, 7, 4'-trihydroxy-8-methoxyflavanone, 5, 7, 4'-trihydroxy-6-methoxyflavanone[20] and Wogonin is reported to exhibit anticancer and anti-inflammatory properties[21]. The root contains rivularin, 2, 5-dihydroxy-6, 7-trimethoxyflavone, 5,7-dihydroxy-8-methoxyflavone, 5-hydroxy-7, 8-dimethoryflavone, 5, 2'-dimethoxy-7, 8, 6'-trimethoxyflavone-2'-O-β-D-glucuronopyranoside, 7-hydroxy-5, 8-dimethoxyflavone-7-O- β -D-glucuronopyranoside, 7-hydroxy-5, 8-dimethoxyflavone-7-O-β-D-glucunopyranoside, 5, 7, 8, 2'-tetrahydroxyflavone-7-O-β-D-glucuronopyranoside and 5, 2', 6'-Trihydroxy-7, 8-dimethoxyflavone-2'-O-β-D-glucuronopyranoside[20]. The average content of total flavonoids present in *S. barbata* is 2.31％, and the leaves contain the highest concentration of total flavonoids followed by tender stems, roots, old stems and flowers as determined by ultraviolet and visible spectrophotometry [22]. Contemporary biomedical experiments have found that flavonoids have significant free radical elimination functions both *in vivo* and *in vitro*[23]. The content of scutellarin is 7.3％-10％, luteolin 0.20％-0.60％, apigenin 0.02％-0.30％ and the other compounds have also been reported to display potent pharmacological activities[20].

2.2 Diterpenoids

Diterpenoids are the other main components of *S. barbata*, from which the scutellones A, B, C, D, E, F, G, H, I and scuterivulactones A, B, C1, C2, D are isolated[22]. Qu et al. identified 30 new neo-clerodane diterpenoid compounds isolated from *S. barbata* from Anhui province of China, including Barbatin C, Scutebarbatine C, Scutebarbatine D, Scutebarbatine E, Barbatin D, Barbatin E, Scutebarbatine K,

Scutebarbatine L, Scutebarbatine O, Scutebarbatine B, Scutelinquanine C, 6-Acetoxybarbatin C, 6-(2, 3-Epoxy-2-isopropyl-n-propoxyl) barbatin C, Barbatin A, Barbatin B, Scutebarbatine G, Scutebarbatine F, 6-O-Nicotinoylscutebarbatine G, 6-O-Nicotinoyl-7-O-acetoxylscutebarbatine G, 6, 7-Di-O-nicotinoylscutebarbatine G, Scutehenanine H, Scutelinquanine D, Scutelinquanine A, Scutebarbatine I, Scutebarbatine J, Scutebarbatine H, 7-O-Nicotinoylscutebarbatine H, Scutebarbatine M, Scutebarbatine N, and Scutelinquanine B[24]. It has been reported recently that the extracts of Scutellaria plants, represented by *S. barbata*, contain antitumor active components, most of which are diterpenoids with specific chemical structure[22]. A new neoclerodane diterpenoid, barbatin H (1) together with fifteen known analogues (2-16) were isolated from *S. barbata*. All of these compounds displayed cytotoxic activities against four human tumor cell lines LoVo (colon cancer), MCF-7 (breast cancer), SMMC-7721 (hepatoma cancer), and HCT-116 (colon cancer) cells by MTT method *in vitro*. The series of neoclerodane diterpenoids exhibited varying degrees of cytotoxic activities against the growth of the tested tumor cell lines, and most of these exhibited selective cytotoxicity against LoVo cell lines. Compound 14 showed significant cytotoxic activities against four tested tumor cells with IC_{50} values of 4.57, 7.68, 5.31 and 6.23 μM, respectively, indicating potential chemotherapeutic use[25].

2.3 Polysaccharides

Polysaccharides are the main class of active constituents required for lymphocyte stimulation and antigen-specific immune response induction by traditional medicinal herbal plants[26]. The polysaccharides present in *S. barbata* are polysaccharides (SBP) : molecular weight 13000, composed of: Rhamnose, Arabinose, Xylose, Mannose, Galactose, Glucose(1.14: 1.5: 0.2: 0.75: 1.0: 2.18); *S. barbata* polysaccharides SPS4: molecular weight 1×10^4, composed of : Rhamnose, Fucose, Arabinose, Xylose, Glucose, Galactose, mannose(0.22: 0.26: 1.0: 0.09: 1.82: 2.09: 0.51)[27]. The SBP isolated by Xu et al[28] from dry whole grass and homogeneity polysaccharides SPS4 isolated by Meng et al. from dry whole grass of *S. barbata* display immunostimulatory and antitumor activity [29].

2.4 Volatile oil

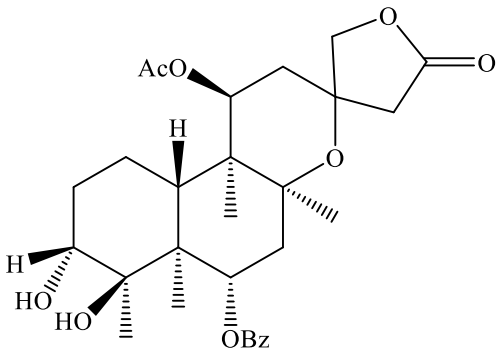
Among the volatile oil of *S. barbata*, oxygenated monoterpene mainly includes menthol, linalool, α-terpineol, thymol; oxygenated sesquiterpene is globulol;

hydrocarbon sesquiterpene mainly includes β-bourbonene, β-himachalene; other compounds with high content are hexahydrofarnesylacetone, 3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol, 1-octen-3-ol, methyleugenol and other 41 compounds have been isolated[18]. Yu et al. have identified 41 components which were extracted by stream distillation and analysed by GC-MS analysis: these volatile components display antimicrobial activity and have the strongest inhibitory effect on Gram-positive bacteria[27]. The Gram-positive bacteria, including methicillin-resistant staphlococcus aureus, were more sensitive to the oil than Gram-negative bacteria and yeasts[30]. Zhang et al. used simultaneous distillation extraction method to extract the volatile oil of the whole grass of *S. barbata* and found relative higher contents of formylofuran (20.53％), thymol (24.10％) and palmitic acid (16.56％), respectively[31].

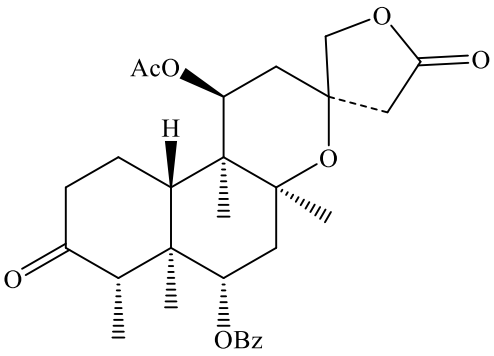
2.5 Other components

Isolation of E-1-4'-hydroxyphenyl-but-1-en-3-one from *S. barbata*, organic acids contain p-Coumaric acid, protoctechuic acid, ursolic acid, stearic acid, and scutellaric acid. *S. barbata* also contains p-hydroxybenzaldehyde and p-hydroxybenzyl acetone[32]. Steroide compounds isolated from *S. barbata* include campesterol, cholesterine, stigmasterol, β-sitosterol, α-sitosterol, soybean steroid-4-alkene-3-ketone, soybean steroid-5, 22-diene-3-alcohol, 4, 4-dimethyl cholesteric-6, 22, 24-triene, ergostane-4, 6,-22-triene-32-alcohol, soybean steroid-3, 5, 22-triene, soybean steroid-5, 22-diene-3-alcohol-ethanoic ester, ergostane-4, 6, 22-triene-3β-alcohol, sitosterol acetate, phytosterin-β-D glucoside, etc[27]. The content of microelements which are essential for human function in the whole grass of *S. barbata* was determined by microwave digestion and flame atomic absorption spectrometry (AAS), and a higher content of Fe, Cu, Zn, Mn, Ca, and Mg [33] which has the highest concentration followed by Fe and Cu and Zn, Mn, etc[32]. The chemical structures of some major types of secondary metabolites have shown in Figure 1.

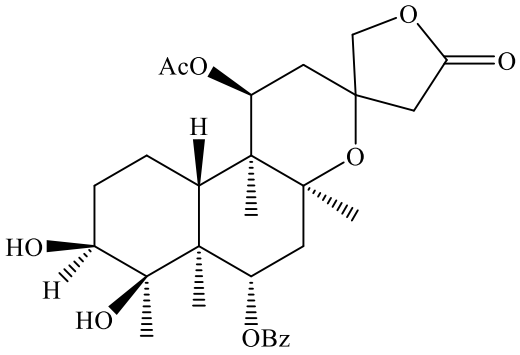
Figure 1: The chemical structures of some major types of secondary metabolites.



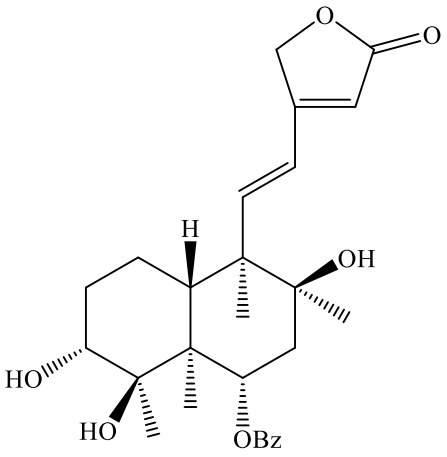
Scutellone A



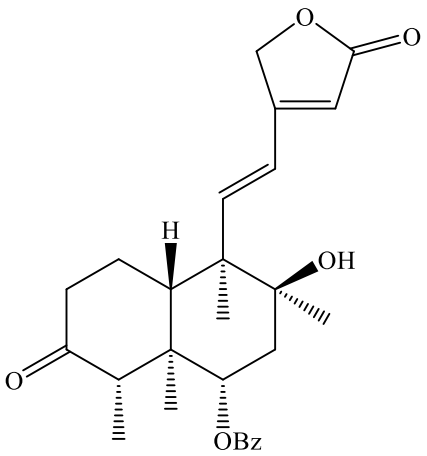
Scutellone B



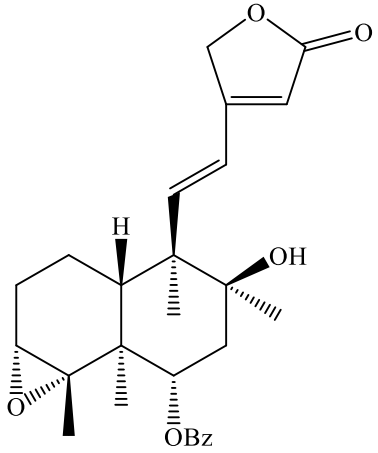
Scutellone C



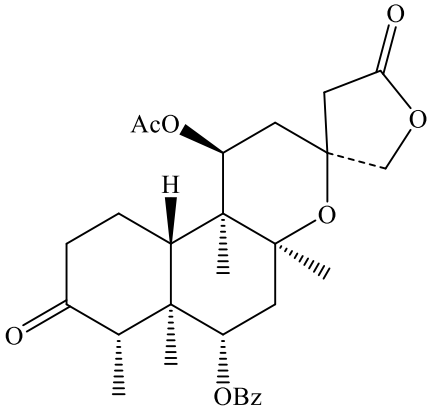
Scutellone D



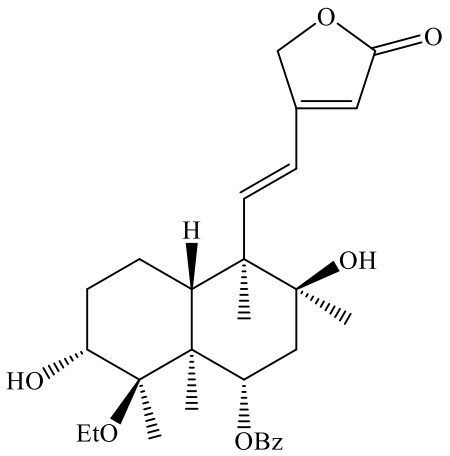
Scutellone E



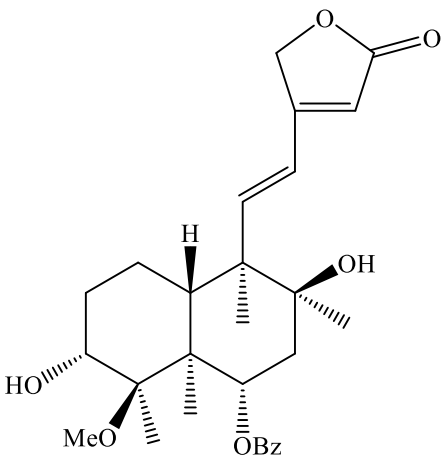
Scutellone F



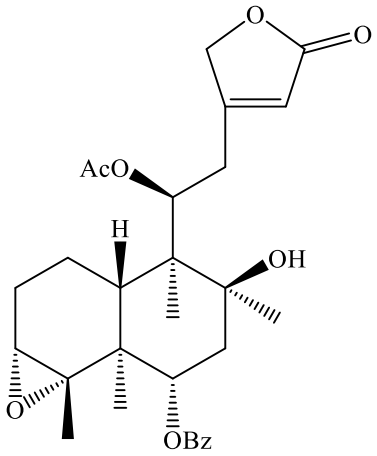
Scutellone G



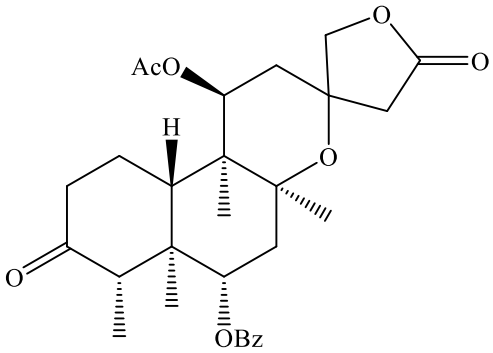
Scutellone H



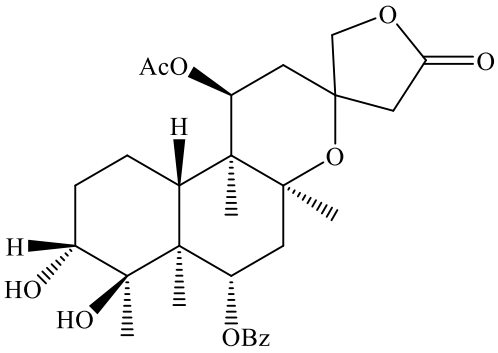
Scutellone I



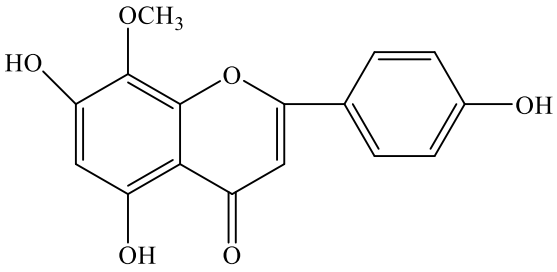
Scuterivulactone A



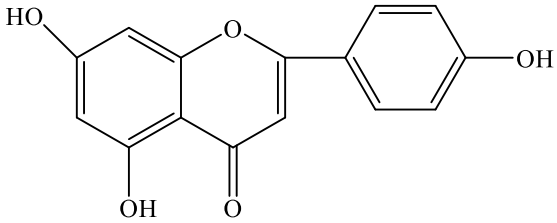
Scuterivulactone B



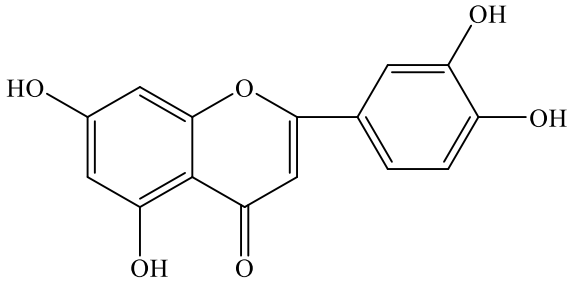
Scuterivulactone C_1



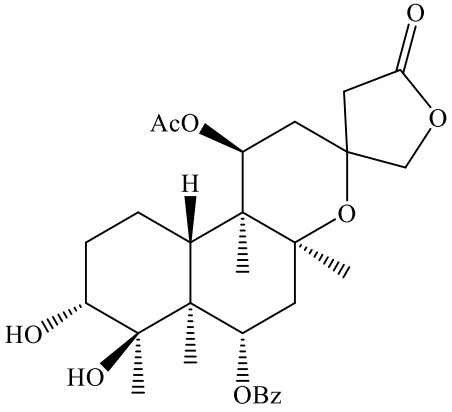
4'-hydroxywogonin



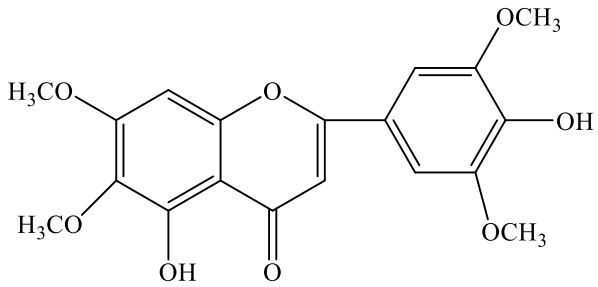
Apigenin



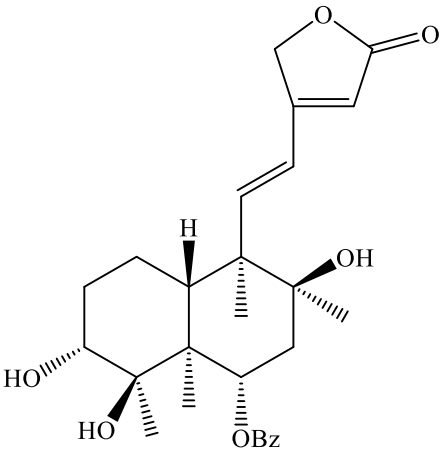
Luteolin



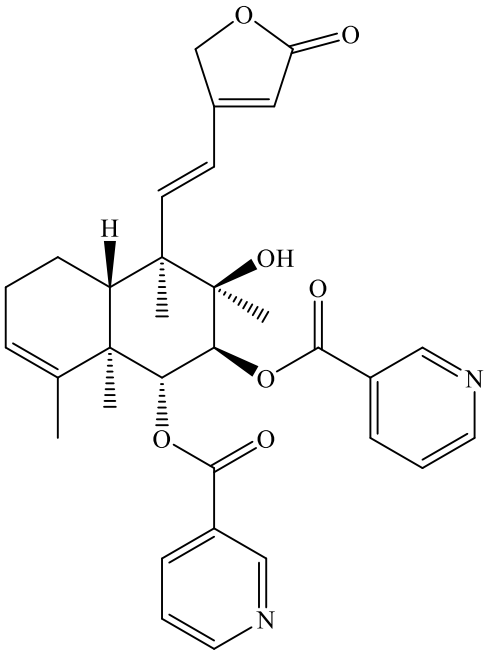
Scuterivulactone C_2



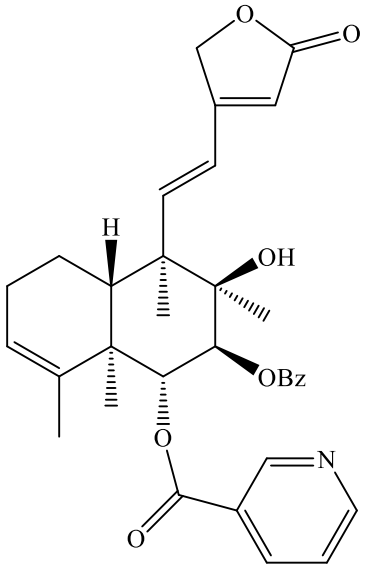
5,4'-dihydroxy-6,7,3',5'-tetramethoxyflavone



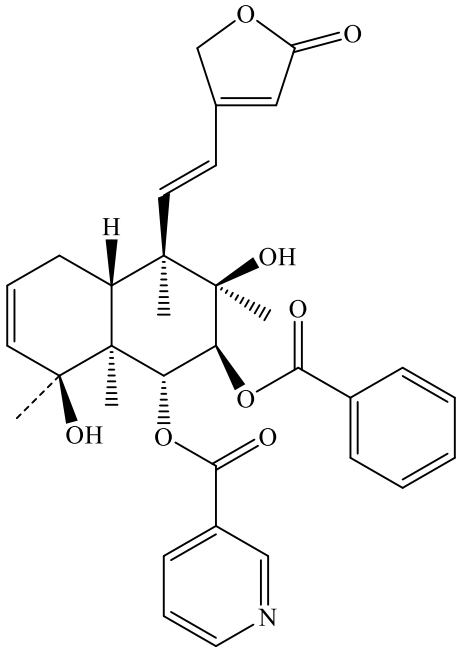
Scuterivulactone D



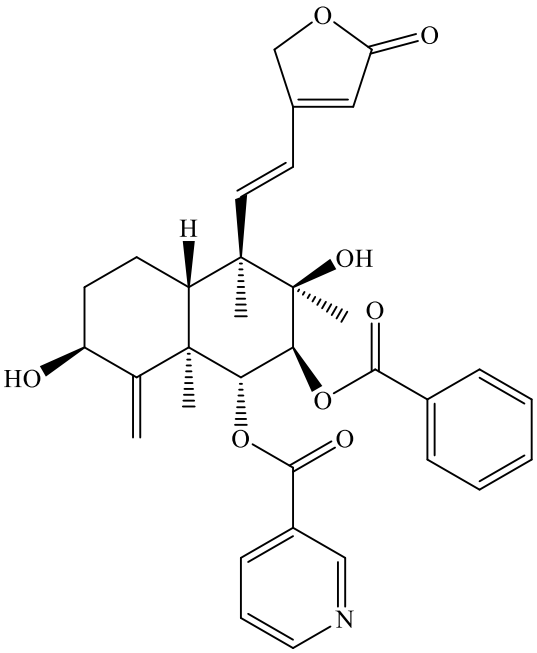
Scutebarbatin A



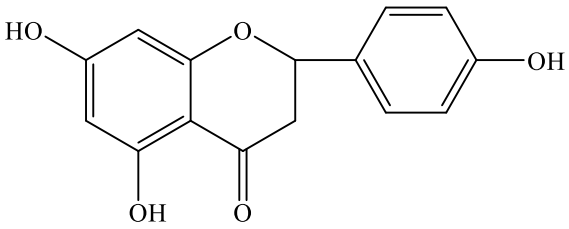
Scutebarbatin B



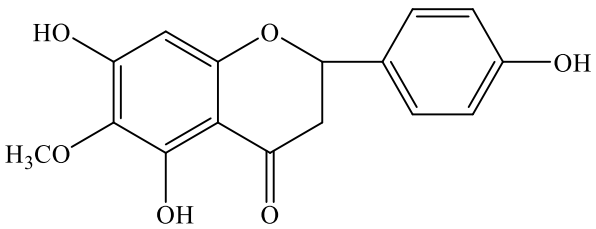
Scutebarbatin C



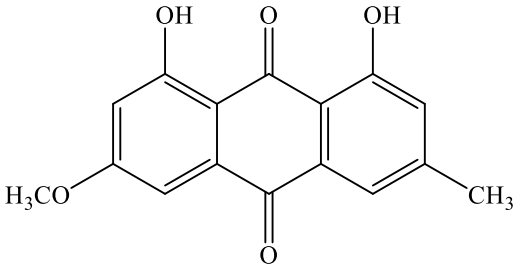
Scutebarbatin D



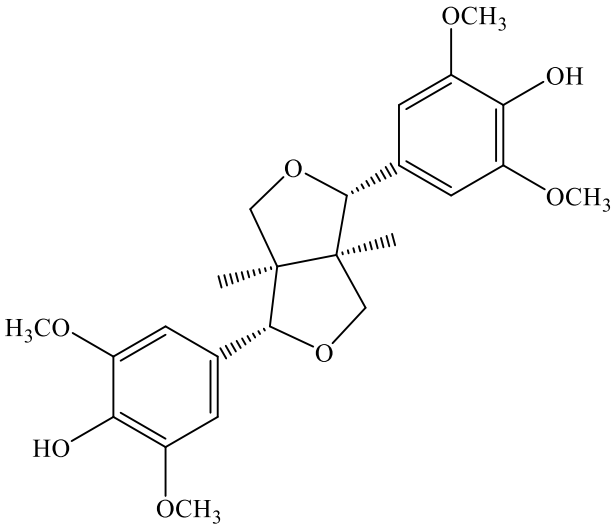
Naringenin



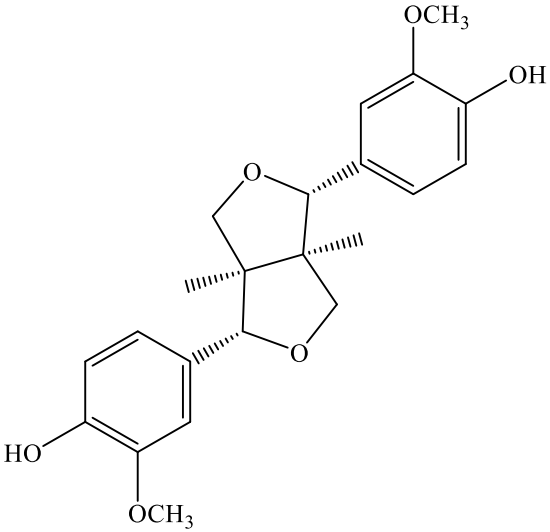
6-methoxynaringenin



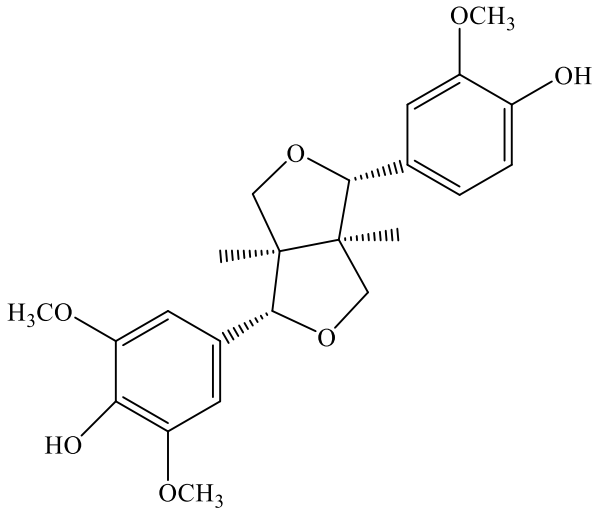
Physcion



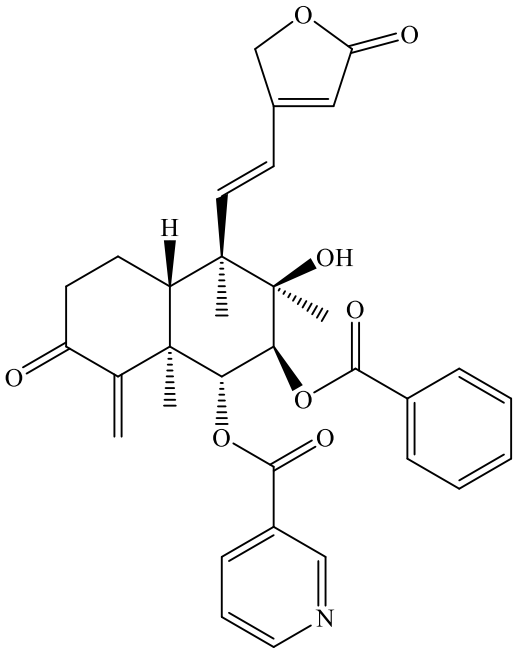
Syringaresinol



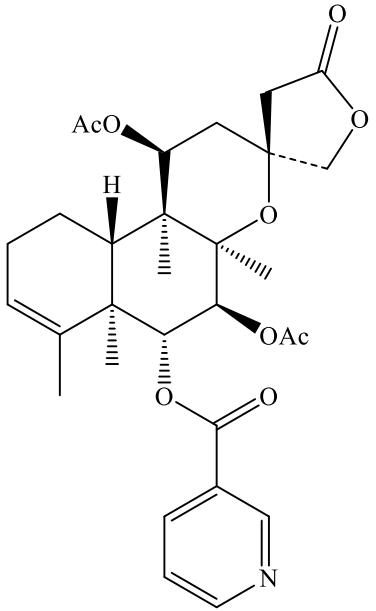
Pinoresinol



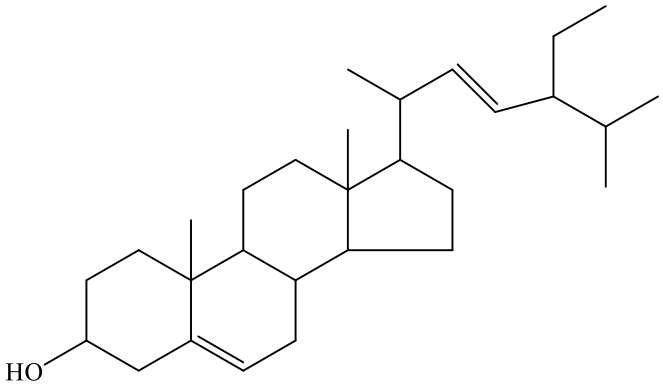
Medioresinol



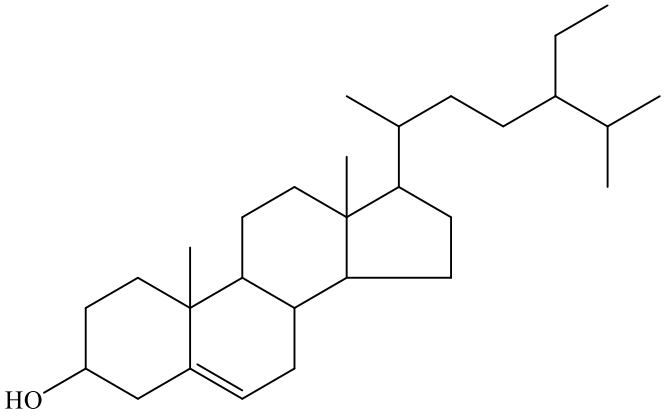
Scutebarbatin E



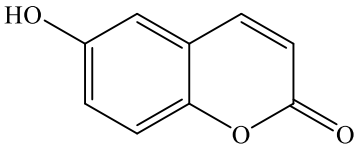
Scutebarbatin F



Stigmasterol



β-sitosterol



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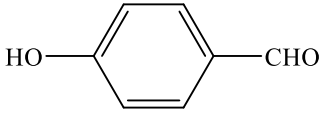
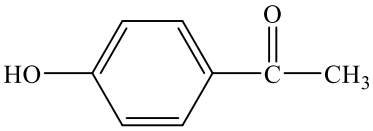
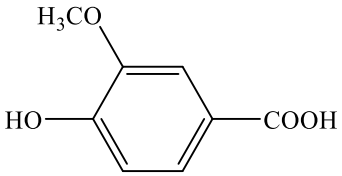


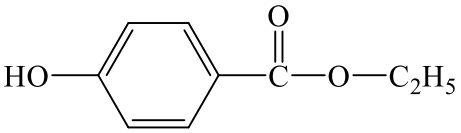
p-hydroxybenzaldehyde



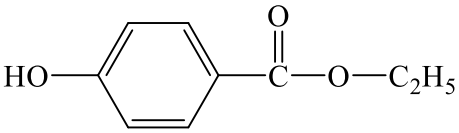
p-hydroxyacetophenone



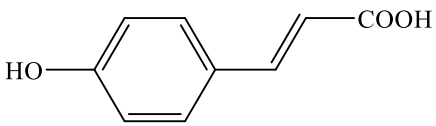
vanillic acid



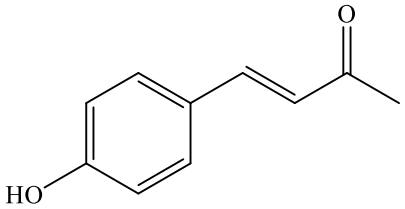
p-hydroxy ethylbenzoate



p-hydroxy ethylbenzoate



p-hydroxycinnamic acid



E-1-(4'-hydroxyphenyl)-but-1-en-3-one

3. Pharmacological activities

3.1 Anti-cardiovascular diseases

I/R injury for example myocardial infarction is the major pathological process in ischemic heart disease. Scutellarin is a flavone isolated from *S. barbata* and Xu et al[34] examined its therapeutic effect on cardiomyocyte I/R injury *in vitro* at doses of 25, 50 and 100 μM, which enhanced JAK2/STAT3-dependent pro-survival signaling and anti-oxidative response, and thus protected cardiomyocytes from I/R injury-induced oxidative stress and apoptosis. Guo et al.[35] has reported the neuroprotective effects of scutellarin both *in vivo* and *in vitro*. *In vivo,* intraperitoneal injections of scutellarin (20 and 60 mg/kg) diminished the percentage of brain infarct volume and enhanced endogenous antioxidant activity. *In vitro*, pretreatment of scutellarin (25, 50 and 100 μM) protected neurons against lethal stimuli, decreased the percentage of apoptotic cells and inhibited reactive oxygen species (ROS). Scutellarin also decreases infarct volume, frequency and distribution of activated microglia and suppresses the production of inflammatory mediators in activated microglia in MCAO rats. It appears to be more potent in its anti-inflammatory effects and exerts its action via TNF-α expression and has proved to be a efficacious therapeutic strategy for the treatment of microglia mediated neurodegenerative diseases [36].

Wogonin, a flavonoid derived from *S. barbata*, has previously been shown to have therapeutic potential for the treatment of atherosclerosis and restenosis. It suppressed the proliferation of vascular smooth muscle cell and inhibited the TNF-α induced MMP-9 secretion through suppression of the transcriptional activity of MMP-9 gene in HASMC[37]. The neuroprotetive effect of wogonin was demonstrated and confirmed by using a permanent model of focal brain ischemia in rats. It reduced the permanent focal ischemic brain injury induced by pMCAO and improved behavioral deficits in rats[38].

Naringenin is another flavonoid present in many plants including *S. barbata*. Naringenin treatment protected against mi/r injury by inhibiting oxidative stress via activation of cgmp-pkgiα signaling[39]. These findings may provide new mechanistic insight into the cardioprotective effects of naringenin, highlighting the opportunity of a novel therapeutic strategy for the patients with ischemic heart disease.

3.2 Anti-tumor activity

3.2.1 Lung cancer

Wogonin, has been reported to exhibit anticancer and antiinflammatory properties. Cyclooxygenase-2 (COX-2) is a key enzyme in the production of prostaglandins in inflammatory conditions[40]. A study investigated the effect of wogonin on phorbol 12-myristate 13-acetate (PMA)-induced COX-2 expression. The results indicated that MEK1/2-AP-1 was very important for PMA-induced COX-2 expression and wogonin inhibited PMA-induced AP-1 activation and c-Jun expression, which is a key component of AP-1[37]. Scutebarbatine A (SBT-A), one of the major alkaloids from *S. barbata*, has a notable antitumor effect on A549 cancer via mitochondria-mediated apoptosis. *In vitro*, SBT-A can significantly inhibit the proliferation of A549 cell lines at concentrations of 20 to 80 μg/mL, up-regulate the expressions of cytochrome c, caspase-3 and 9, and down-regulate the levels of Bcl-2 in A549 cells. *In vivo*, intraperitoneal injection of SBT-A (40 mg/kg) to mice resulted in a significant suppression of tumor growth [41].

Polysaccharides isolated from *S. barbata*（PSB）at doses of 10, 20, 40 and 80 μg/ml potently inhibited cell proliferation and human epidermal growth factor receptor (HER) 2 phosphorylation *in vitro. In vivo*, PSB displayed significant antitumor activity through reducing microvessel density in a Calu-3 subcutaneous xenograft model at doses of 100 mg/kg and 200 mg/kg administered intraperitoneally once daily[42]. The treatment with 0.5 mg/ml *S. barbata* triggered P38/SIRT1-regulated cell apoptosis through G_2/M phase arrest and ER stress-, intrinsic mitochondrial-, and extrinsic FAS/FASL-mediated pathways in CL1-5 tumor cells. *In vivo*, i.p. injection of *S. barbata* (60 mg/kg) significantly reduced tumor size with decreased proliferation and angiogenesis, as well as increased apoptosis and autophagy in CL1-5 tumor bearing mice[43].

3.2.2 Liver cancer

S. barbata at an oral dose of 6, 3 and 1.5 g/d per kg of body weight when given to rats inhibited the proliferation of H22 cells in a time-dependent manner. The extract also induced apoptosis of H22 cells via losing their mitochondrial transmembrane potential, releasing mitochondrial cytochrome C into cytosol and increasing caspase-3 activity in a dose-dependent manner[44].

Metastasis is the major cause of cancer-related deaths and targeting this process has been proposed as a strategy to fight cancer[45]. Dai et al. investigated the anti-metastatic effect of total flavonoids of *S. barbata* (TF-SB). The results showed that TF-SB (20, 40, 60, 80, 100, 120 and 140 μg/mL) significantly inhibited the activity of proliferation and invasion and reduced the metastatic capability of MHCC97H cells in a dose-dependent manner, probably through decreasing the MMP expression and increasing the TIMP expression[11]. *S. barbata* extract also inhibited the proliferation of HepG2 cells *in vitro* at the doses of 0.05, 0.1, 0.2, 0.3, and 0.5 mg/mL and suppressed the tumor growth of hepatoma H22-bearing mice at the doses of 50, 100, and 150 mg/kg/day by intragastric administration. Meanwhile, it increased NK cells' cytotoxicity in spleen, down-regulated the amount of $CD^{4+}CD^{25+}Foxp^{3+}$ Treg cells and Th17 cells in tumor tissue, and decreased IL-10, TGF-β_1, and IL-17A levels whereas increased IL-2 and IFN-γ levels in the serum of hepatoma H22-bearing mice[46].

3.2.3 Colorectal cancer

The ethanol extract of *S. barbata* (EESB) at doses of 0.5, 1.5 and 2.5mg/ml significantly inhibited the IL-6-mediated increase in STAT3 phosphorylation and transcriptional activity in HT-29 human colon carcinoma cells, resulting in the suppression of cell proliferation and the induction of apoptosis[47]. EESB at doses of 0.125, 0.25, 0.5, 1, 1.5 and 2 mg/ml significantly reduced HCT-8 cell viability, attenuated the migration and invasion ability of HCT-8 cells in a dose-dependent manner, decreased the expression levels of MMP-1, MMP-2, MMP-3/10, MMP-9, MMP-13, phosphoinositide 3-kinase (PI3K)/AKT and transformed growth factor (TGF)-β/Smad [48].

Angiogenesis, which plays a critical role during tumor development, is tightly regulated by the Sonic Hedgehog (SHH) pathway known to malfunction in many types of cancer[49]. Inhibition of angiogenesis via modulation of the SHH signaling pathway has become very attractive for cancer chemotherapy and it might be one of the mechanisms by which *S. barbata* was effective in the treatment of cancers[50]. The intra-gastric administration with 2g/kg of EESB reduces tumor size without increase in body weight in CRC mice. EESB treatment suppressed the expression of key mediators of the SHH pathway in tumor tissues, which in turn resulted in the inhibition of tumor angiogenesis. Furthermore, EESB treatment inhibited the expression of vascular

endothelial growth factor A (VEGF-A), an important target gene of SHH signaling and functioning as one of the strongest stimulators of angiogenesis[51].

3.2.4 Gastric adenocarcinoma

S. barbata had a dose-dependent cytotoxic effect on MKN-45 cells. Treatment with the ethanol extract of *S. barbata* inhibited the proliferation and promoted the apoptosis of human gastric adenocarcinoma cells by modulating the caspase-, MAPK- and ROS-dependent pathway[1].

3.2.5 Ovarian cancer

The extract of *S. barbata* (0, 100, 200, 400 μg/ml) reduced the viability of ovarian cancer A2780 cells and induced apoptosis by down-regulating Bcl-2 protein expression and increasing Caspase 3/9 proteins expression. Furthermore, the migration activity of A2780 cells was significantly inhibited and the underlying mechanism is probably related to the decrease of MMP-2/9[52].

3.2.6 Leukemia

The treatment with various concentrations (0.2, 0.5, and 1.0 mg/ml) of *S. barbata* extract (SBE) resulted in apoptosis of HL-60 cells by an increase in sub-G_1 phase cells, DNA fragmentation and degradation of the inhibitory protein for the caspase-activated deoxyribonuclease[53]. The methylene chloride extract of *S. barbata* (MCSB) inhibited the proliferation of human U937 leukemia cells in a dose-dependent manner (IC_{50}=10 μg/ml), and increased the sub-G_1 DNA content. Caspase-9 and caspase-3 were activated by MCSB while caspase-8 was intact. Similarly, MCSB effectively cleaved PARP, increased the ratio of Bax/Bcl-2 and the release of the cytochrome c from mitochondria, causing apoptosis in U937 cells[54].

3.2.7 Other tumors

BZL101, an aqueous extract from the *S. barbata* plant, inhibited reproductive cancer growth in many cell lines by regulating expression levels of key cell cycle components that differ with respect to the cancer cell phenotypes, such as early stage estrogen sensitive MCF7 cells, early stage androgen sensitive LNCap cells, late stage hormone insensitive breast cancer MDA-MB-231 cells and prostate cancer pC3 cells [55]. In male TRansgenic adenocarcinoma of mouse prostate mice were given *S.*

barbata extract orally at a dose of 8, 16, or 32 mg/kg and the prostate tumor progression was delayed as determined by histological assessment[56].

S. barbata also inhibited the growth of leiomyomal cells (LM) in a time-dependent manner. Pregnant Sprague-Dawley rats were administered drinking water containing 20g/L or 50g/L of *S. barbata* extract. The results indicated that the extract reduced the expression of Bcl-2 protein in human uterine leiomyoma cells enhanced by progesterone[57]. TF-SB (40, 80, 120,160 or 200 μg/ml) inhibited the proliferation, migration and invasion of MDA-MB-231 cells in a dose-dependent manner. *In vivo*, TF-SB prevented bone metastasis of breast cancer cells in a dose-dependent manner, but did not affect tumor growth or mouse survival. Molecular analysis revealed that TF-SB controlled the secretion of osteolysis-related factors PTHrP and its downstream ranKl/oPG[58].

3.3 Antibacterial activity

S. barbata extract displays antibacterial effects both *in vitro* and *in vivo*. The bacterial load showed a significant decrease in the lungs of the XDRAB pneumonia murine which received the oral *S. barbata* extract (200 mg/kg) in comparison to the control group[59]. In addition, the histopathological examination also revealed better resolution of perivascular, peribronchial, and alveolar inflammation in the *S. barbata* extract-treated group. The ability to affect multiple target signaling pathways is a potential mechanism of action and might be related to its efficacy of removing heat and counteracting toxicity[60]. The essential oil of *S. barbata* displayed a broad antimicrobial spectrum and exerted a stronger bactericidal effect against gram-positive bacteria, including methicillin-resistant S. aureus (MRSA). The antimicrobial activity of the oil was possibly related to menthol and long chain alcohols such as linalool and 1-octen-3-ol, menthol has been reported to have significant antimicrobial activity[61]. Linalool has been demonstrated to have strong inhibitory effect against 17 bacteria and 10 fungi. In fact, long chain (C6-C10) alcohols were particularly active against gram-positive bacteria, and the antimicrobial properties of alcohols are known to increase with molecular weight[62]. According to recent studies, community-acquired or outpatient MRSA infections are increasing in both children and adults, MRSA is responsible for worldwide outbreaks of nosocomial infections. The essential oil of *S. barbata is* a potential source of novel antimicrobial essential oils[60].

3.4 Antiviral activity

Neo-clerodane diterpenoids were reported to have significant inhibitory effect on EBV lytic replication. Bioassay-guided fractionation was conducted on an EtOAc-soluble extract of the whole plant of *S. barbata*, monitored by inhibition of Epstein-Barr virus (EBV) lytic replication[63].

3.5 Anti-inflammatory activity

Liu et al. reported *S. barbata* anti-inflammatory activity in RAW 264.7 cells. Both ethanol and ethyl acetate extracts at the doses of 50, 100, 200 mg/mL significantly inhibit the production of lipopolysaccharide-induced nitric oxide, prostaglandin E_2, interlukin-6, and interlukin-1β, as well as the expression of phosphor extracellular signal-regulated kinase and phosphor-c-Jun N-terminal kinase (p-JNK)[64].

3.6 Antioxidant activity

Superoxide radical is a highly toxic species which can be generated by numerous biological and photochemical reactions. In addition to directly attacking important biological molecules, superoxide radical may also decompose to form singlet oxygen and hydroxyl radicals, which may increase local oxidative stress and initiate cellular damage or lipid peroxidation and pathological incidents such as arthritis and Alzheimer's disease[65]. Superoxide scavenging activities of polysaccharides from *S. barbata* (SBP) was found to increase with increasing concentrations, and the superoxide radical scavenging rate of SBP at 1.0 mg/ml was 67.1％. The IC_{50} value for eliminating superoxide was 0.17 mg/ml, indicating that the polysaccharides had a significant superoxide radical scavenging activity[66].

3.7 Anti-MDR activity

Scutellarin, scutellarein and 5,7,4'-trihydroxy-8-methoxy flavanone, flavonoids isolated from *S. barbata,* enhanced the response of CDDP-resistant human OVCAR-3 cells to CDDP. Cell viability was around 95% and 53% respectively when treated with scutellarin, but the viability was dramatically decreased to about 17% when treated with the combination of these two compounds, demonstrating a significant synergistic effect[67]. The extract of *S. barbata* (ESB) was able to enhance the sensitivity of MKN-

45 cells to chemotherapeutic agents *in vitro*. ESB suppressed cell growth more than each flavonoid used alone when combined with several chemotherapeutic agents, especially cisplatin, etoposide, or doxorubicin, suggesting that ESB increases the chemo-sensitivity of MKN-45 cells[1].

3.8 Alleviation of memory deficits and neuronal injuries

Treatment with *S. barbata* flavonoids at dose of 35-140 mg/kg reduced the memory impairment and neuronal injury induced by composited Aβ, including neuron loss or pyknosis in hippocampus, typical colliquative necrosis in cerebral cortex, mitochondrial swelling and cristae fragmentation and a large number of lipofuscin deposits in the cytoplasm[68].

3.9 Insecticidal activity

1-hydroxynaphthalene from *S. barbata* oil and its derivatives might be effective natural agents for the management of house dust and storage mites. Based on the LD_{50} values of 1-hydroxynaphthalene derivatives against D. farinae, D. pteronyssinus, and T. putrescentiae, the acaricidal activity of 1-hydroxynaphthalene (2.11, 2.37, and 4.50 μg/cm^2) was 4.76, 6.00, respectively. [69].

4. Toxicology

Li et al. reported the toxicity observation of large dose of *S. barbata*（120g） in prescriptions. The results showed that no significant changes before and after treatment were observed, indicating the safe use of large quantities[70].

5. Clinical application

5.1 Tumor

50 cases with advanced non-small cell lung cancer were treated with the compound of *S. barbata* and other Chinese medicines with kidney-tonifying efficay and another 50 patients in the control group received NP chemotherapy[71]. The results showed that the improvement rate of quality of life after 3 years was 66% in the treatment group and 36% in the control group ($P<0.01$). Although the effective rate of 18% in the treatment group for short-term treatment was lower than 60% in the control group ($P<0.01$), the myelosuppression rate of 6% was also lower than 48% in the

control group (P<0.01). A retrospective analysis showed that among 375 patients treated with *S. barbata*, the total effective rate was 58.62% (220 cases) [72]. Xiaoji Decoction composed of *S. barbata*, *Curcuma Zedoary*, *Hedyotis Diffusa*, *Java Brucea*, *Selfheal*, *Radix Sophorae Flavescentis*, *Astragalus Mongholicus* and *Red Ginseng* had a sensitizing effect on cisplatin chemotherapy and thermochemotherapy, improving the curative effect of low-concentration and low-dose chemotherapeutic drugs[73]. Compared with the use of chemotherapy alone, Xiaoji Decoction greatly reduced the toxicity and side effects of chemotherapeutic drugs, thus improving the chemotherapy tolerance of patients. After 32 ovarian cancer cases were treated with the compound Tuyuan Decoction containing *S. barbata*, the total effective rate was 75％[74]. This prescription has many anticancer effects, such as inhibiting tumor angiogenesis, inducing apoptosis of cancer cells, killing cancer cells, enhancing immunity. The tumor continued to shrink, immunity was enhanced, adverse reactions were small, and no granulocytopenia, liver and kidney function damage and other serious reactions were noticed. After treatment with *S. barbata* prescription plus interventional therapy, the effective rate of 90.6% for 32 cases with various malignant tumors including liver cancer, gastric cancer, and esophageal carcinoma was higher than 74.2% in the control group treated with interventional therapy alone (P＜0.005) [75].

5.2 Hepatitis

105 cases with Hepatitis B were treated with Yi-Gan-Fang decoction containing *S. barbata* and 60 cases taking western medicine as control. The results showed the effective rate of alleviating main symptoms in the treatment group was higher than that in the control group (P < 0.05). The difference in ALT and TBiL levels was significant between the two groups (P < 0.05), and the negative change of HBeAg HBV-DNA was significantly different between the two groups also (P < 0.05) [76]. 78 hepatitis liver fibrosis cases were treated with Ruan-Gan powder containing *S. barbata.* The results showed the clinical symptoms were alleviated and liver function and HA, LN, PCIII of liver fibrosis parameters recovered in the treatment group. The abnormal index of CIV was significantly improved in the treatment group compared with the control group (P < 0.05) [77].

5.3 Gastropathy

61 patients with precancerous lesions of chronic atrophic gastritis were treated with Qilian-Shupi granule[78]. The total effective rate was 80.3% in the treatment group and 70.0% in the control group ($P < 0.05$). The clinical symptom score, gastric mirror image, pathological curative effect, pathological score and inhibition of H. pylori in the treatment group were significantly different from those in the control group ($P < 0.01$, $P < 0.05$). After treatment, serum SOD increased and LPO decreased significantly. When *S. barbata* and *Hedyotis Diffusa* were combined with other Chinese medicines to treat 87 cases with chronic gastritis, the cure rate was 89.7% and the effective rate was 100%[79]. The total effective rate was 83.3%, when 30 chronic atrophic gastritis cases were treated with Yiwei Decoction containing *S. barbata*[80].

5.4 Gynecological diseases

Guo et al. [81] used antibiotics to control infection, and the Traditional Chinese Medicine prescription (*Field Pennycress*， *Scutellaria Barbata*, *Dandelion*, *Radix Paeoniae Rubrathe*, *Peach Kernel*, etc.) was added to treat 96 cases with chronic pelvic inflammatory disease simultaneously. Of 96 cases, 71 were cured, 25 were improved, the cure rate being 73.96%. Yiqing Decoction（*Codonopsis Pilosula*，*Astragalus Mongholicus*，*Raw Semen Coicis*, *Alisma Orientalis*, *Scutellaria Barbata*）was taken orally and meanwhile Man-pen NO.1 decoction was applied by enema for 56 cases with chronic pelvic inflammatory disease. The total effective rate was 89.3% in the treatment group compared to that of 59.3% in the control group ($P < 0.01$) [82].

5.5 Nephropathy

Yangyin decoction containing *S. barbata* was applied to treat Henoch-Schonlein purpura nephritis[83]. The treatment group of patients received Yangyin Decoction (n=30) and the control group of received Glucosidorum Tripterygll Totorum tablets (n=30). The total effective rate was significantly higher in the treatment group than that in the control group ($P < 0.05$). The treatment group was superior to the control group in controlling the clinical symptoms and improving the indexes of laboratory examination ($P < 0.05$ or $P < 0.01$). Yiqi-Huoxue-Jiangzhuo prescription was used to treated 48 patients with chronic renal failure[84]. The total effective rate in the treatment group was 91.67% compared to that of 75.0％in the control group ($P < 0.05$).

5.6 Prostatic diseases

Zhang et al.[85] treated 60 cases of chronic prostatitis with the Decoction combined with *S. barbata*. The results showed that 38 cases were cured, 18 cases improved, and 4 cases were unresponsive, the total effective rate being 93.3%. Zhang et al.[86] also applied Qilong Decoction containing *S. barbata* to treat 55 cases of senile prostatic hypertrophy. The results showed that 45 cases were cured, 8 cases improved, and 2 cases were unresponsive, the total effective rate being 96.36%.

5.7 Other diseases

Wang [74] retrospectively analyzed clinical data of 375 patients treated with *S. barbata*. 168 patients with urinary blood were treated with Ban-zhi-lian decoction comprised of *S. Barbata*, *Astragalus Bunge*, *Rhizoma Anemarrhenae*, *Rhizoma Imperatae*, *Golden Cypress* and *Eclipta Alba* as a basic drug. 62 cases of urinary calculi were treated by Huayu-Paishi decoction composed of *S. Barbata*, *Desmodium*. *S. Barbara*, *Semen Celosiae*, and *Radix Salviae Miltiorrhizae* as main medicine. *S. barbata* eye drops were applied to treat 56 cases of viral keratitis. Total effective rate in patients treated with *S. barbata* were 58.62% (17 cases), 100.00% (81 cases), 96.77% (146 cases), 86.90% (60 cases) and 94.64% (53 cases), respectively.

6. Conclusion

S. barbata is commonly used in clinic for clearing away heat, detoxification, anti-cancer, and as an anti-inflammatory agent. The chemical constituents mainly contain flavonoids, diterpenoids, alkaloids, steroids, etc. *S. barbata* can treat cardiovascular and cerebrovascular diseases by improving the blood supply of cardio-cerebrovascular system via activating the blood vessels of human body and making the blocked blood vessels unobstructed. Recent pharmacological studies have shown that *S. barbata* possesses anti-tumor, anti-virus, bacteriostasis and anti-inflammatory effects, indicating very high medicinal value. At present, *S. barbata* capsule and tablets are produced in the domestic market for the treatment of the pharyngalgia caused by acute pharyngitis. Recent studies focusing on molecular targets of plant derived chemical constituents have yielded promising results, but the details of the mechanisms involved need to be clarified further. Even though some effective plant derived drugs have been

developed from *S. barbata,* there still remains an untapped resource in it. Therefore, numerous constituents deserve further investigations *in vitro* and *in vivo* due to their significant pharmacological activity.

Table 1. Compounds isolated from *Scutellaria barbata*

Classification	Chemical component	Part of plant	Ref.
1. Flavanoids			
1.1 Flavone	Moslosooflavone	Root	[87]
	7-hydroxy-5-methoxy flavonoid	Root	[88]
	7-hydroxy-5, 8-dimethoxyflavone	Aboveground part	[20]
	Chrysin	Whole herb	[18]
	Wogonin	Aboveground part	[20]
	5, 7-dihydroxyl-8, 2'-dimethoxy flavone	Whole herb	[18]
	Panicolin	Whole herb	[18]
	Rivularin	Root	[20]
	Anisomelin	Whole herb	[89]
	7, 2'-dyhydroxyl-5, 8-dimethoxy flavone	Whole herb	[18]
	Baicalein	whole herb	[90]
	5, 6, 2'-trihydroxyl-7, 8-dimethoxy flavone	Whole herb	[18]
	2'-hydroxychrysin	Whole herb	[18]
	Scutevulin	Root	[18]
	Apigenin	Aboveground part	[20]
	Hispidulin	Aboveground part	[20]
	4'-hydroxywogonin	Aboveground part	[20]
	Scutellarein	whole grass	[91]
	5, 7,8, 4'-tetrahydroxyl flavone	whole grass	[18]
	5, 7, 2', 3'-tetrahydroxyl flavone	whole grass	[92]

	Luteolin	Aboveground part	[20]
	5, 7, 8, 2’-tetramethyl flavone	whole grass	[18]
	5, 7, 8, 4’-tetramethyl flavone	whole grass	[18]
	5, 7, 8, 2’, 6’-pentamethoxyl flavone	whole grass	[18]
1.2 Flavonone	Naringenin	Aboveground part	[20]
	5, 7, 4’-trihydroxy-6-methoxyflavonone	Aboveground part	[20]
	5, 7, 4’-trihydroxy-8- methoxyflavonone	Aboveground part	[20]
	Carthamidin	whole grass	[19]
	Isocarthamidin	whole grass	[19]
	Eriodictyol	Aboveground part	[20]
1.3 Flavonoid glycoside	5-hydroxyl-7, 8, 2’-trimethoxy flavones-6’-o-β-d-glucoside	whole herb	[18]
	7-hydroxy-5,8-dimethoxyflavone-7-O-β-D-glucuronopyranoside	Root	[20]
	5, 2’-dyhydroxyl-7, 8-dimethoxy flavones-6’-o-β-d-glucoside	whole grass	[18]
	5, 2’-dyhydroxyl-7, 8, 6’-trimethoxy flavones-2’-o-β-d-glucoside	Root	[20]
	5, 2’, 6’-trihydroxy-7, 8-dimethoxyflavone-2’-O-β-D-glucuronopyranoside	Root	[20]
	Scutellarin	whole herb	[19]
	5, 8, 4’-trihydroxy-7-o-β-d-glucoside	whole herb	[18]
	5, 7, 8, 2’-tetrapydroxyflavone-7-O-β-D-glucuronopyranoside	Root	[20]
2. Diterpenoids	Scutellone A	whole herb	[93]

	Scutellone B	whole herb	[93]
	Scutellone C	whole herb	[93]
	Scutellone D	whole herb	[93]
	Scutellone E	whole herb	[93]
	Scutellone F	whole herb	[93]
	Scutellone G	whole herb	[93]
	Scutellone H	whole herb	[93]
	Scutellone I	whole herb	[93]
	Scuterivalactone A	whole herb	[18]
	Scuterivalactone B	whole herb	[18]
	Scuterivalactone C_1	whole herb	[18]
	Scuterivalactone D	whole herb	[18]
	Scuterivalactone C_2	whole herb	[18]
3. Alkaloid	Scutebarbatins A	whole herb	[94]
	Scutebarbatins b	whole herb	[95]
	Scutebarbatins c	whole herb	[96]
	Scutebarbatins d	whole herb	[96]

	Scutebarbatins e	whole herb	[96]
	Scutebarbatins f	whole herb	[96]
4. Steroide	Campesterol	whole herb	[97]
	Cholesterine	Root	[97]
	Stigmasterol	Root	[97]
	B-sitosterol	Root	[97]
	Gamma-sitosterol	whole herb	[97]
	Soybean steroid-4-alkene-3-ketone	whole herb	[97]
	Stigmasta-5, 22-dien-3-ol	whole herb	[97]
	Cholesta-6, 22, 24-trien, 4, 4-dimethyl-	whole herb	[97]
	Ergosta-4, 6,-22-trien-3.alpha-ol	whole herb	[97]
	Stigmastan-3, 5, 22-trien	whole herb	[97]
	Stigmasta-5, 22-dien-3-ol, acetate	whole herb	[97]
	Erogosta-4, 6, 22-trien-3.beta.-ol	whole herb	[97]
	Sitosterol acetate	whole herb	[97]
	Phtosteryl-β-D- glucoside	whole herb	[98]
5.Other	Polysaccharide	whole herb	[28]

components			
	Volatile oil	whole herb	[31]
	Scutellaric acid	whole herb	[99]
	P-Cournaric acid	whole herb	[20]
	Protoctechuic scid	whole herb	[20]
	Ursolic acid	whole herb	[20]
	Stearic acid	whole herb	[97]
	Microelements	whole herb	[33]
	E-1-4’-hydroxyphenyl-but-1-en-3-one	whole herb	[99]
	P-hydroxybenzaldehyde	Aboveground part	[20]
	P-hydroxybenzylacetone	Aboveground part	[20]

Table 2. Summary of Pharmacological activities of *S. barbata*

Sort	Effective part or phytochemicals	Observation	Cell type	Activity	Mechanism of action	Ref.
Lung cancer	SBT-A Methanol Extract	In vitro 20-80μg/ml In vivo 40mg/kg	A549	Inhibited proliferation Inhibited tumor growth	Up-regulated the expression of cytochrome c, caspase-3 and 9, and down-regulated the levels of Bcl-2 in A549 cells	[41]
	PSB Aqueous Extract	In vitro 10-80μg/ml	Calu-3	Inhibited proliferation	Inhibited human epidermal growth factor receptor (HER)2 phosphorylation, downregulated the expression of the downstream signaling molecules	[42]
	SB Methanol Extract	In vitro 0.5-2.0mg/ml In vivo 60mg/kg	CL15	Induced apoptosis Inhibited proliferation and angiogenesis Increased apoptosis and autophagy	P38/SIRT1-regulated cell apoptosis through G2/M phase arrest and ER stress-, intrinsic mitochondrial-, and extrinsic FAS/FASL-mediated pathways	[43]
Liver cancer	ESB Aqueous Extract	In vitro 1.5, 3or6g/d per kg	H22	Inhibited proliferation and induced apoptosis	ESB-treated cells rapidly lost their mitochondrial transmembrane potential, released mitochondrial cytochrome C into cytosol, and induced caspase-3 activity	[44]

	TF-SB Ethanol Extract	In vitro 20-140 µg/ml	MHCC97H	Inhibited proliferation and invasion	Decrease of the MMP expression, and simultaneous increase of the TIMP expression	[11]
	SBE Aqueous Extract	In vitro 0.05-0.5mg/ml In vivo 50-150mg/kg	HepG2	Inhibited proliferation Inhibited tumor growth	Down-regulation of Treg cells and manipulating Th1/Th17 immune response	[46]
		In vitro 0.5-2.5mg/ml	HT-29	Inhibited proliferation and induced apoptosis	Modulated the IL-6/STAT3 signaling pathway and its target genes	[47]
Colorectal cancer	EESB Ethanol Extract	In vitro 0.125-2mg/ml	HCT-8	Inhibited proliferation, migration and invasion	Suppressed PI3K/AKT and TGF-β/Smad signal pathways	[48]
		In vivo 2g/kg	HT-29	Induced apoptosis and angiogenesis	Suppressed the expression of key mediators of the SHH pathway	[49]
Gastric adenocarcinoma	ESB Ethanol Extract	In vitro 40-200µg/ml	MKN-45	Induced apoptosis and inhibited proliferation	Modulated the caspase-, MAPK- and ROS-dependent pathway	[1]

Ovarian Cancer	SB Ethanol Extract	In vitro 100-400µg/ml	A2780	Induced apoptosis	Down-regulated Bcl-2 protein and increased Caspase 3/9 proteins	[52]
	SBE Aqueous Extract	In vitro 0.2-1.0mg/ml	HL-60	Inhibited cell growth and induced apoptosis	Downstream of the CDK inhibitory protein-CDK/cyclin cascade, SBE decreased phosphorylation level of retinoblastoma protein	[53]
Leukemia	MCSB Methanol Extract	In vitro 10-90µg/ml	U937	Inhibited proliferation and induced apoptosis	Increased the sub-G1 DNA contents. Caspase-9 and caspase-3 were activated while caspase-8 was intact by MCSB. Cleaved PARP, increased the ratio of Bax/Bcl-2 and released the cytochrome c from mitochondria	[54]
Reproductive cancers	BZL101 Aqueous Extract	In vitro 2.0mg/ml	MCF7	Inhibited proliferation	Induced a G1 cell cycle arrest and ablated expression of key G1 cell cycle regulators Cyclin D1, CDK2 and CDK4, growth factor stimulatory pathways and estrogen receptor-α expression.	[55]
	SB Aqueous Extract	In vivo 1mg/ml	LNCaP	Induced apoptosis	Elevated expression of Bax, p53, Akt, and JNK	[56]

	TF-SB Ethanol Extract	In vitro 40-200μg/ml	MDA-MB-231	Inhibited proliferation, migration and invasion	Controlled the expression of PTHrP and its downstream OPG/RANKL	[6]
Uterine leiomyoma	SB Aqueous Extract	In vitro 20-40μg/ml	LM	Inhibited proliferation	Reduced the expression of Bcl-2 protein	[57]
Antibiosis	SB Aqueous Extract	In vivo 200mg/kg	XDRAB	Decreased bacterial load in the lungs	Affected multiple target signaling pathways and their potential mechanisms of action	[58]
Anti-viruses	Neo-clerodane diterpenoids Ethanol Extract	In vitro 3.2-23.6μg/mL	EBV	Inhibited lytic replication	Not investigated	[59]
Anti-inflammation	SB Ethanol or Ethyl Acetate Extract	In vitro 50-200mg/mL	RAW 264.7	Anti-inflammatory activity toward RAW 264.7 cells	Inhibited the production of lipopolysaccharide-induced nitric oxide, prostaglandin E2, interlukin-6, and interlukin-1β, inhibited the expressions of phosphor extracellular signal-regulated kinase and phosphor-c-Jun N-terminal kinase(p-JNK),	[64]

Antioxidant	SBP Aether Extract	In vitro 0.17-1.0 mg/ml	Superoxide	Scavenged radical superoxide activity.	Not investigated	[61]
Anti-MDR	Scutellarin Ethanol Extract	In vitro 60 μM	OVCAR-3	Enhanced sensitization to cisplatin	Correlated with the positions of hydroxyl group and methoxygroup of flavonoids	[62]
Prevent myocardial I/R injury	Scutellarin Ethanol Extract	In vitro 25-100μMol/L	H9C2	Suppressed cardiomyocytes damage	Enhanced JAK2/STAT3-dependent pro-survival signaling and anti-oxidative response, and thus protected cardiomyocytes from I/R injury-induced oxidative stress and apoptosis	[68]
Immunocompetence	Protein Polysaccharide Aqueous Extract	In vitro 1-50μg/mL	Splenocyte	Enhanced lymphocyte proliferation	Stimulated the production of IFN-c in the splenocyte cultures	[69]

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